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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
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WASHINGTON, DC 20005

| EXAMINER | |
|---|---|
| NGUYEN, QUANG | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | 15 |

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/880,887 | NEGRIER ET AL. | |
| | Examiner | Art Unit | |
| | Quang Nguyen, Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 December 2002 and 04 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *7-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11* is/are rejected.

7)☒ Claim(s) *7-10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/526,935* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicants' amendments filed on 12/23/02 and 6/4/03 have been entered as Paper Nos. 11 and 14, respectively.

Amended claims 7-11 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

### *Terminal Disclaimer*

The terminal disclaimer filed on 12/23/02 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,271,025 has been reviewed and is accepted. The terminal disclaimer has been recorded.

### *Claim Objections*

Claim 7 is objected to because the phrase "Factor VIII cDNA is modified by deletion of the B-domain" is not technically correct. This is because the B-domain of the Factor VIII protein is made up of the amino acids, whereas Factor VIII cDNA is composed of nucleotides. The phrase - - Factor VIII cDNA is modified by deletion of the B-domain encoded sequence - - would obviate this objection. Appropriate correction is required.

Claim 8 is objected to because the phrase "Factor VIII cDNA is modified by replacement of the B-domain" is not technically correct. This is because the B-domain of the Factor VIII protein is made up of the amino acids, whereas Factor VIII cDNA is composed of nucleotides. The phrase - - Factor VIII cDNA is modified by replacement of the B-domain encoded sequence - - would obviate this objection. Appropriate correction is required.

***Following is a new ground of rejection necessitated by Applicants' amendment.***

***Written Description***

Amended claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a process for producing a Factor VIII protein, said process comprises introducing splice sites into a wild-type Factor VIII cDNA, then inserting one or more introns into the wild-type cDNA containing splice sites, followed by introducing into a cell the modified cDNA for the production of the protein wherein the yield of the protein produced with the modified cDNA is greater than the yield produced with wild-type Factor VIII cDNA. The instant claim encompasses the introduction of any intron into any location of Factor VIII cDNA, so that upon introducing the modified cDNA into a cell the yield of the Factor VIII protein produced with the modified cDNA is greater than that produced with a wild-type cDNA. Apart from the disclosure that the insertion of a truncated intron I of factor IX having SEQ ID NO:9 into a cDNA encoding a factor VIII lacking the B domain at one or more specific sites where factor VIII introns were spliced (e.g., intron I, intron 12, intron 13) results in a significant better production of factor VIII in CHO cells and HepG2 cells relative to the unmodified cDNA, the instant specification fails to teach a representative number of introns and/or modified cDNAs having the recited functional limitation, so that upon introducing a cell the yield of the Factor VIII protein encoded by the modified cDNAs is greater than the yield produced with the unmodified cDNAs. The instant specification fails to teach the essential core structural elements possessed or shared by a broad genus of introns that confer the modified cDNAs an ability to yield of greater production of the Factor VIII protein in a cell relative to the unmodified cDNAs. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of

Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a broad genus of introns other than the truncated factor IX intron 1 of SEQ ID NO. 9, whose incorporation at any locations of a Factor VIII cDNA construct would endow the modified cDNA construct an ability to produce the results contemplated by Applicants (e.g., a greater production of Factor VIII protein produced by the modified cDNA than the production produced by the unmodified cDNA), and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Response to Amendment***

Applicants' arguments related to the above rejections in the Amendment filed on 12/23/02 in Paper No. 11 (page 9) have been fully considered.

Applicants simply argue that claim 11 has been amended to a process for producing a Factor VII protein, and that the specification discloses three examples of the claimed process for producing a Factor VII protein from a modified Factor VIII cDNA and each of which demonstrates a higher protein yield than does wild-type Factor VIII cDNA.

Applicants' arguments are respectfully found to be unpersuasive because the specification (including the three examples) simply teaches the use of the truncated Factor IX intron 1 of SEQ ID NO:9 for the construction of modified Factor VIII cDNAs to yield the desired results. What are the essential core structural elements possessed or shared by a broad genus of introns whose incorporation into any locations of Factor VIII cDNA would confer the modified Factor VIII cDNAs an ability to yield of greater production of the Factor VIII protein in a cell relative to the unmodified cDNAs? The instant specification fails to teach a representative number of introns and/or modified Factor VIII cDNAs having the recited functional limitations.

Accordingly, claim 11 remains rejected for the reasons set forth above.

***Claim Rejections - 35 USC § 112***

Amended claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A process for producing a Factor VIII protein comprisising:

a) preparing a modified Factor VIII cDNA, wherein said Factor VIII cDNA is modified by deletion of the B-domain encoded sequence or replacement of the B-domain encoded sequence with nucleotides encoding four arginines, and an insertion of the truncated Factor IX intron 1 (SEQ ID NO:9) in one or more splice sites of the Factor VIII cDNA;

b) introducing the modified Factor VIII cDNA into a cell; and

c) expressing the modified Factor VIII cDNA in said cell to produce the protein, wherein the yield of the protein produced with modified Factor VIII cDNA is greater than the yield produced with a wild-type Factor VIII cDNA;

does not reasonably provide enablement for a process for producing a Factor VIII protein using a modified Factor VIII cDNA that has been modified by introducing splice sites into a wild-type Factor VIII cDNA at any locations, and inserting any intron into the splice sites, so that upon introducing the modified cDNA into any cell, the yield of the Factor VIII protein produced with the modified cDNA is greater than the yield produced with the unmodified cDNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

*Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claim is drawn to a process for producing a Factor VIII protein comprising: a) obtaining a wild-type cDNA of the Factor VIII protein; b) introducing splice sites into the wild-type cDNA; c) preparing a modified Factor VIII cDNA by inserting one or more introns from one or more additional cDNAs into the wild-type cDNA; d) introducing the modified Factor VIII cDNA into a cell; and e) expressing the polypeptide encoded by the modified Factor VIII cDNA in the cell to produce the protein, wherein the yield of the protein produced with modified Factor VIII cDNA is greater than the yield produced with wild-type Factor VIII cDNA.

The specification teaches by exemplification showing the insertion of a truncated intron 1 of factor IX having SEQ ID NO:9 into a cDNA encoding a factor VIII lacking the B-domain, at one or more specific sites where factor VIII introns were spliced (e.g., intron I, intron 12, intron 13) results in a significant better production of factor VIII in CHO cells and HepG2 cells relative to the unmodified cDNA. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

***(a) The breadth of the claim.*** The instant claim encompasses a process for producing a Factor VIII protein using a modified Factor VIII cDNA that has been modified by introducing splice sites into a wild-type Factor VIII cDNA at any locations, and inserting any intron into the splice sites, so that upon introducing the modified cDNA

into any cell, the yield of the Factor VIII protein produced with the modified cDNA is greater than the yield produced with the unmodified cDNA.

***(b) The state and the unpredictability of the art.*** At the effective filing date of the present application, little was known on the role of any intron in the expression of a wild-type Factor VIII cDNA in any cell, let alone for enhancing the expression of Factor VIII protein. Kurachi et al. (J. Biol. Chem. 270:5276-5281, 1995) have attributed the presence of splicing sequences (splice acceptor site, splice donor site, branch site) of human factor IX intron 1 for higher levels of expression of factor IX from the minigene constructs in a cultured cell system, rather than the presence of enhancer like elements within the intron (see abstract). The physiological art is recognized as unpredictable (MPEP 2164.03).

***(c) The amount of direction or guidance presented.*** Apart from disclosing the insertion of a truncated intron 1 of factor IX having SEQ ID NO:9 into a cDNA encoding a factor VIII that lacks the B domain at one or more specific sites where factor VIII introns were spliced (e.g., intron I, intron 12, intron 13) results in a significantly better production of factor VIII in CHO cells and HepG2 cells relative to the unmodified cDNA, the instant specification fails to provide sufficient guidance for a skilled artisan on the use of any introns and their insertion into splice sites (It is noted that **Sal I site** is considered by Applicants as a splice site, see Amendment C page 8, line 17-19) at any location on the wild-type Factor VIII cDNA (having an intact B domain encoded sequence), such that upon introducing the modified cDNA into a cell, the yield of the Factor VIII protein produced with the modified cDNA is greater than the yield produced

with the unmodified cDNA. The exemplifications show that there is a great variation in the yields of factor VIII produced even using modified cDNAs having a specific truncated intron I of IX of SEQ ID NO:9 into a cDNA encoding a factor VIII that lacks the B domain at one or more specific sites where factor VIII introns were spliced (e.g., FVIII I1+13; FVIII I12 and FVIII I1). For example, with the modified cDNA construct of FVIII I12, there is no FVIII protein produced in HepG2 cells (see example 4.2, Fig. 5); the amounts of mRNA and intracellular protein levels for cells transfected with FVIII, FVIII I1 and FVIII I1+12 constructs are very similar and significantly less than those observed for the FVIII I1+13 construct (see Figs. 6 & 7). Thus, it appears that the high level of expression of Factor VIII protein from the exemplified modified Factor VIII cDNAs in any cell has to be determined empirically, even though they contain the same truncated Factor IX intron 1 of SEQ ID NO:9, and it is inserted at positions in place of Factor VIII introns, let alone for the incorporation of any intron into any splice sites (e.g., **Sal I** site) being introduced at any locations on a wild-type Factor VIII cDNA (without the deletion of the encoded B domain sequence) to yield the desired results. There is no evidence of record indicating that splicing sequences derived from any Factor IV introns are functionally equivalent with respect to enhanced expression of Factor VIII cDNA as the splicing sequences present in the Factor IX intron I of SEQ ID NO:9, let alone for those derived from any intron, including the **Sal I** splice site as contemplated by Applicants. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so.

With the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Additionally, as set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

With respect to the breadth of the instant claim, particularly the utilization of any intron for enhancing the production of Factor VIII polypeptide in any cell, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

The courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the

breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the method as claimed.

***Response to Amendment***

Applicants' arguments related to the above rejections in the Amendment filed on 12/23/02 in Paper No. 11 (pages 9-10) have been fully considered.

Applicants simply argue claim 11 has been amended to a process for producing a Factor VIII protein, and that the specification discloses three examples of the claimed process for producing a Factor VIII protein from a modified Factor VIII cDNA and each of which demonstrates a higher protein yield than does wild-type Factor VIII cDNA. These examples provide a high level of guidance such that there will be no undue experimentation.

Applicants' arguments are respectfully found to be unpersuasive because all exemplified modified Factor VIII cDNAs contain the same truncated Factor IX intron I of SEQ ID NO:9, and it is inserted at positions in place of Factor VIII introns, in addition to the deletion of an encoded B-domain sequence in these modified cDNAs. Furthermore, NOT all modified cDNA constructs have been demonstrated to produce a yield of Factor VIII protein greater than the yield produced with wild-type Factor VIII cDNA in any cell (see example 4.2, Fig. 5). Given the state of the prior art, the unpredictability of the physiological art, the lack of sufficient guidance provided by the instant specification as discussed above, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

## *Conclusion*

***No claims are allowed.***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

*Quang Nguyen, Ph.D.*

DAVID GUZO
PRIMARY EXAMINER